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# MECHANISM OF ACTION OF (-)CATHINONE, A NEW ALKALOID FROM KHAT LEAVES

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**Abstract** — A new alkaloid, (-)cathinone, has recently been isolated from khat leaves and has been shown to induce amphetamine-like behavioural effects. The actions of this alkaloid at the cellular level are discussed here and it is concluded that (-)cathinone resembles amphetamine in influencing catecholamine release both centrally and peripherally. As it is likely that the central and peripheral symptoms observed during khat consumption are due to these effects of (-)cathinone, it can be assumed that the widespread habit of khat chewing is pharmacologically analogous to amphetamine abuse.

## INTRODUCTION

Because of their stimulant effect, fresh leaves of the khat shrub are chewed habitually by many people in East Africa and the Arab Peninsula. The consumption of khat causes sympathomimetic effects and induces symptoms such as euphoria and hyperactivity (Halbach, 1972). The tendency of many khat users to obtain their daily supply of the drug by any means is a clear manifestation of psychic dependence.

Recently, the new alkaloid (-)cathinone (chemically α-amino-propiophenone) has been isolated from khat leaves and has been reported to produce pharmacological effects that closely resemble those of amphetamine, for example anorexia (Zelger and Carlini, 1980), hyperthermia (Kalix, 1980a), and hypermotility (WHO Advisory Group, 1980; Zelger *et al.*, 1980; Kalix, 1980b; Valterio and Kalix, 1982). In all these respects the alkaloid has been found to have a potency similar to that of (+)amphetamine. The experiments whose results are described and discussed in the present article were designed to find out if (-)cathinone acts also at the cellular level by a mechanism resembling that of amphetamine.

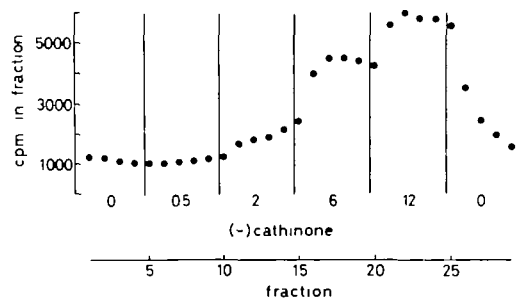


Fig. 1. Effect of increasing concentrations of (-)cathinone on the efflux of radioactivity from rabbit striatal tissue prelabelled with $^3$H-dopamine. Each fraction corresponds to 3 min of efflux. For details see Kalix (1981).

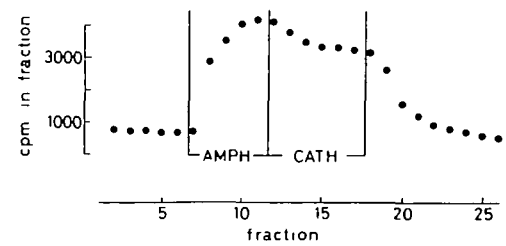


Fig. 2. Effect of 3 μM (+)amphetamine and of 6 μM (-)cathinone on the efflux of radioactivity from rabbit striatal tissue prelabelled with $^3$H-dopamine. For details, see Kalix (1981)

## RESULTS AND DISCUSSION

The effect of (-)cathinone on the efflux of radioactivity from rabbit striatal slices pre-

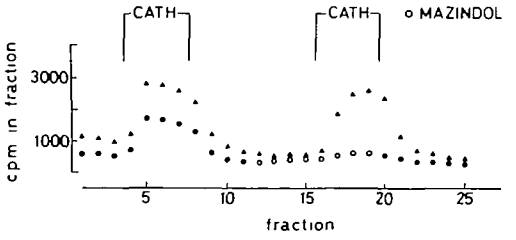


Fig. 3. The effect of mazindol on the (-)cathinone-induced release of radioactivity from rabbit striatal tissue prelabelled with $^3$H-dopamine. Two preparations from the same animal were superfused in parallel and stimulated twice with 10 μM (-)cathinone during 12 min. Before and during the second stimulation the test preparation ( ● ) was superfused for 24 min ( ○ ) with 1 μM mazindol. The efflux from the control preparation is indicated by triangles. For details, see Kalix (1982).

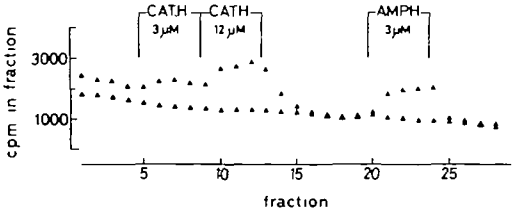


Fig. 4. The effect of (-)cathinone and (+)amphetamine on the release of radioactivity from rat nucleus accumbens tissue prelabelled with $^3$H-dopamine. The efflux from an unstimulated control preparation superfused simultaneously is indicated by open triangles. For details, see Kalix (1982).

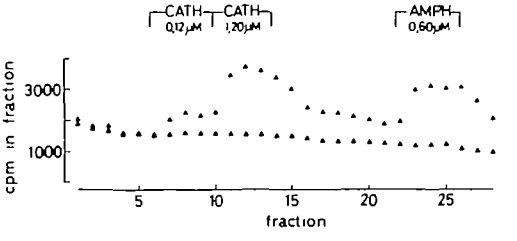


Fig. 5. Effect of (-)cathinone and of (+)amphetamine on the efflux of radioactivity from rabbit atrium tissue prelabelled with $^3$H-noradrenaline The efflux from an unstimulated control preparation superfused simultaneously is indicated by open triangles. Each fraction corresponds to 3 min of efflux. For details see Kalix (1983).

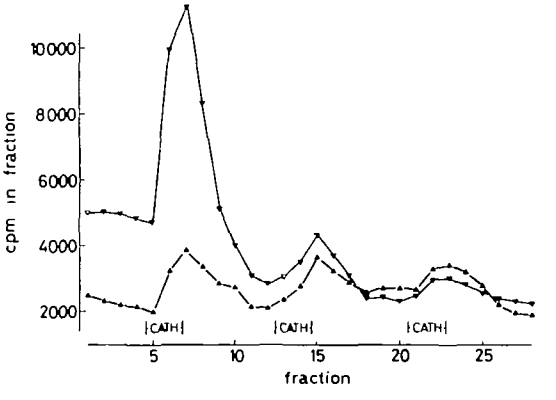


Fig. 6. Repetitive stimulation with 0.80 μM (-)cathinone of the efflux of radioactivity from rabbit atrium tissue obtained from untreated ( ▲ ) or reserpinized ( ▽ ) animals and prelabelled with $^3$H-noradrenaline. Reserpine (Serpasil®) was injected intramuscularly 20hr before the experiment at a dose of 2 mg/kg. For details, see Kalix (1983).

labelled with $^3$H-dopamine was examined. It was found that low concentrations of (-)cathinone enhanced the release of label in a dose-dependent manner (Fig. 1), and that (-)cathinone was capable of sustaining the enhanced release induced by (+)amphetamine (Fig. 2).

Pretreatment of the tissue with mazindol, which is known to prevent the induction of release by (+)amphetamine, inhibited the efflux increase caused by (-)cathinone (Fig. 3). In further experiments with dopamine-prelabelled tissue, the new alkaloid was found to cause release also from the nucleus accumbens (Fig. 4), a brain region thought to be critically involved in the locomotor response to amphetamine. Taken together, these observations suggest that (-)cathinone is a central stimulant with a mechanism of action analogous to that of amphetamine.

Characteristically, the consumption of khat is accompanied by sympathomimetic effects, especially at the cardiovascular level. Therefore, it was subsequently investigated if the releasing effect of (-)cathinone observed in the CNS occurred also in peripheral tissues. When slices of rabbit atria that had been prelabelled with $^3$H-noradrenaline were superfused with solutions of either (-)cathinone or (+)amphetamine, a rapid increase in efflux of radioactivity was observed (Fig. 5). In tissue obtained from reserpinized animals the releasing effect of (-)cathinone, as well as that of (+)amphetamine, was characterized by rapid development of tachyphylaxis (Fig. 6).

The results of the experiments described here indicate that (-)cathinone has an amphetamine-like releasing effect at central dopaminergic synapses as well as at peripheral noradrenaline storage sites. As it is likely that the central and peripheral symptoms observed during khat consumption are due to this effect of the alkaloid, it can be concluded that the widespread habit of chewing khat is pharmacologically analogous to amphetamine abuse.

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